SGLT2 inhibitors and kidney outcomes by glomerular filtration rate and albuminuria: A Collaborative Meta-Analysis

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Key Points (limit 100 words)

Question: Do the kidney protective effects of SGLT2 inhibitors vary by estimated glomerular filtration rate (eGFR) or albuminuria?

Findings: In this meta-analysis that included 70,361 participants in 10 trials of SGLT2 inhibitors vs. placebo, SGLT2 inhibitors significantly reduced progression of chronic kidney disease (CKD), serious acute kidney injury, and kidney failure. The relative risk reduction for CKD progression was consistent regardless of eGFR and albuminuria. Significant reductions in the annual rate of eGFR decline were observed across all subgroups, including when participants with and without diabetes were analysed separately.

Meaning: These findings support the routine use of SGLT2 inhibitors to improve kidney outcomes across the full spectrum of kidney function and albuminuria among patients with type 2 diabetes, CKD or heart failure.

Importance

Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce chronic kidney disease (CKD) progression in individuals with type 2 diabetes, CKD, or heart failure. However, their effects in those with stage 4 CKD or little to no albuminuria remain uncertain.

Objective

To assess whether estimated glomerular filtration rate (eGFR) or degree of albuminuria, as measured by urinary albumin-to-creatinine ratio (UACR), modifies the effects of SGLT2 inhibitors on kidney outcomes.

Data sources

SGLT2 inhibitor trials participating in the SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium (SMART-C).

Study selection

Randomized, double-blind, placebo-controlled trials within SMART-C evaluating an SGLT2 inhibitor with label indications for reducing CKD progression and at least 500 participants in each arm and at least six months of follow-up.

Data extraction and synthesis

Treatment effects in individual trials were pooled using inverse variance weighted meta-analysis.

Main outcomes and measures

CKD progression, defined as kidney failure, ≥50% reduction in eGFR, or death due to kidney failure. Other outcomes included annual rate of eGFR decline and kidney failure.

Results

Among 70,361 participants (mean [SD] age 64.8 [8.7] years; 24,595 (35.0%) female) in 10 randomized trials, 2,314 (3.3%) experienced CKD progression and 988 (1.4%) reached kidney failure. SGLT2 inhibitors reduced the risk of CKD progression (25.4 vs. 40.3 events per 1000 patient-years; HR 0.62, 95% CI 0.57–0.68), irrespective of baseline eGFR (in mL/min/1.73 m^2): ≥60 (HR 0.61, 95% CI 0.52–0.71), 45–<60 (HR 0.57, 95% CI 0.47–0.70), 30–<45 (HR 0.64, 95% CI 0.54–0.75), and <30 (HR 0.71, 95% CI 0.60–0.83; P-trend=0.16), and baseline

albuminuria (in mg/g): ≤30 (HR 0.58, 95% CI 0.44–0.76), >30–300 (HR 0.74, 95% CI 0.57–0.96), and >300 (HR 0.57, 95% CI 0.52–0.64; P-trend=0.49). While the magnitude of protection varied, SGLT2 inhibitors reduced the annual rate of eGFR decline across all eGFR and UACR subgroups, including when participants with and without diabetes were analysed separately. SGLT2 inhibitors also reduced the risk of kidney failure alone (HR 0.66, 95% CI 0.58-0.75).

Conclusion and relevance

In this meta-analysis, SGLT2 inhibitors were found to lower the risk of CKD progression regardless of baseline eGFR or albuminuria, including in patients with stage 4 CKD or minimal albuminuria, supporting their routine use to improve kidney outcomes across the full spectrum of kidney function among patients with type 2 diabetes, CKD or heart failure.

Introduction

Sodium glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of kidney disease progression, cardiovascular events, and mortality in patients with type 2 diabetes, chronic kidney disease (CKD), or heart failure.[1] As a result, major clinical practice guidelines now recommend their use in these populations.[2-4]

Because their glucose-lowering efficacy declines at lower estimated glomerular filtration rate (eGFR) and due to concerns about the risk of precipitating acute kidney injury (AKI), the use of SGLT2 inhibitors – originally developed as glucose-lowering agents – has historically been restricted in patients with lower eGFR.[5] Although regulatory thresholds for initiation have been revised in recent years, routinely collected data from health systems worldwide indicate that patients with lower eGFR remain less likely to receive an SGLT2 inhibitor.[6] Accordingly, patients with advanced CKD (eGFR <30 mL/min/1.73m²) were underrepresented in most SGLT2 inhibitor trials, and real-world uptake in this group is particularly limited, despite their markedly elevated risk of kidney failure and cardiovascular disease.

Additionally, several guidelines offer varying recommendations on the use of SGLT2 inhibitors in CKD based on albuminuria: Based on completed outcomes trials and their inclusion criteria, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines give a strong recommendation (1A) for SGLT2 inhibitor use in patients without type 2 diabetes and UACR ≥200 mg/g, compared with a weaker recommendation (2B) for those with UACR <200 mg/g.[2] Similarly, in the United Kingdom, the National Institute for Health and Care Excellence (NICE) offers varying recommendations for individuals with type 2 diabetes based on UACR thresholds of 30 mg/g and 300 mg/g.[7] These discrepancies are reflected across several implementation documents and guidelines,[8,9] highlighting ongoing uncertainty about whether the kidney-protective effects of SGLT2 inhibitors vary according to baseline albuminuria levels.

To address these uncertainties, we conducted a collaborative meta-analysis of trials participating in the SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium to evaluate the impact of eGFR and albuminuria on the kidney protective effects of SGLT2 inhibitors.

Methods

The SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium (SMART-C) comprises completed randomized, double-blind, placebo-controlled outcome trials with at least 500 participants in each treatment arm and follow-up of at least six months.[1] The Consortium is led by an academic steering committee comprising representatives from each of the participating trials. A systematic review was not performed. This analysis was restricted to trials within SMART-C evaluating SGLT2 inhibitors with a label indication for CKD progression (canagliflozin, dapagliflozin, and empagliflozin). Trials in which longitudinal kidney outcomes were not systematically collected were excluded.

This meta-analysis is one of two SMART-C companion analyses. The current study focuses on the effects of SGLT2 inhibitors on kidney outcomes across the full spectrum of eGFR and albuminuria, while the companion meta-analysis summarizes the net absolute benefits of SGLT2i on kidney, cause-specific hospitalization and cause-specific mortality outcomes by diabetes status and albuminuria.[10] Both were reported according to the PRISMA statement.[11]

This meta-analysis includes data from 10 trials (Figure S1): four trials enrolled participants with type 2 diabetes at high atherosclerotic cardiovascular risk (EMPA-REG OUTCOME, CANVAS Program and DECLARE-TIMI 58),[12-14] four trials studied participants with heart failure across the spectrum of ejection fraction (EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF and DELIVER),[15-18] and three were primary kidney outcome trials (CREDENCE, DAPA-CKD, EMPA-KIDNEY).[19-21] Protocols for each of the included trials were approved by relevant ethics committees and all participants provided written informed consent. SGLT2

inhibitor trials participating in SMART-C, evaluating effects in the post-myocardial infarction setting (DAPA-MI and EMPACT-MI) were not included because longitudinal kidney outcomes were not systematically recorded.[22,23] Trials of sotagliflozin, an SGLT1/2 inhibitor, and ertugliflozin were also excluded since these agents do not have a label indication for kidney outcomes. Risk of bias was assessed by the SMART-C Secretariat (BLN and HJLH) using the Cochrane Risk of Bias 2 Tool.

Outcomes

The primary outcome in this meta-analysis was CKD progression, defined as kidney failure, ≥50% reduction in eGFR, or death due to kidney failure. Kidney failure was defined as dialysis, kidney transplantation, or eGFR<15 mL/min/1.73m^2. Secondary clinical outcomes included: (1) kidney failure, ≥50% reduction in eGFR, or death due to cardiovascular disease or kidney failure; (2) kidney failure; (3) kidney failure or all-cause mortality; and (4) serious AKI. AKI was defined based on investigator reported adverse events (using the Medical Dictionary for Regulator Activities term “acute kidney injury), and restricted to those identified as serious adverse events (i.e. life-threatening, leading to, or prolonging, hospitalization, or causing persistent or significant disability).

Additionally, we evaluated effects on the annualized rate of decline in eGFR (eGFR slope) as a secondary outcome.[24] Analysis of eGFR slope provides additional statistical power compared to clinical outcomes to evaluate effects on kidney function across eGFR and UACR subgroups. Because SGLT2 inhibitors cause an acute, hemodynamic reduction in eGFR that differs from their long-term effect, we evaluated outcomes over distinct time periods. The acute effect was defined as the change in eGFR from treatment initiation to the first post-randomization assessment (typically within three months). Chronic eGFR slope was defined as the difference in annualized rate of eGFR decline between treatment and placebo, calculated from the first post-randomization measurement until end of follow-up. We also

evaluate total eGFR slope, incorporating all eGFR measurements from randomization to end of study.

Subgroups

We evaluated treatment effects according to baseline eGFR (<30, 30-<45, 45-<60, and ≥60 mL/min/1.73m^2) and UACR (<30, 30-300, and >300 mg/g) categories. Additionally, we combined eGFR and UACR using the KDIGO classification of CKD into low, moderate, high, and very-high risk categories. We further examined whether the effects of SGLT2 inhibitors on kidney outcomes are modified by eGFR, UACR and KDIGO risk categories separately in patients with and without diabetes. While there were very few participants with eGFR <20 mL/min/1.73m2 at randomization based on the lower eGFR thresholds for trial entry, we divided the subgroup with eGFR <30 mL/min/1.73m^2 into 20 to <30 and <20 mL/min/1.73m^2 in exploratory analyses to examine treatment effects in these individuals in whom treatment initiation is not currently recommended by guidelines.

Statistical analysis

We conducted a two-stage meta-analysis, with outcome definitions harmonized across trials, in line with previous SMART-C collaborative meta-analyses.[1,25,26] Treatment effects were obtained from individual trials and pooled using inverse variance weighted meta-analysis. Two trials (DAPA-HF and DELIVER) recorded eGFR at baseline but not UACR. These trials were included in overall treatment effect estimates and subgroup analyses by baseline eGFR, since all participants had the opportunity to have eGFR evaluated at baseline, but were excluded from subgroup analyses by baseline UACR. Data were independently verified at the trial level by each collaborating group and subsequently subjected to central quality control by two authors at the SMART-C data coordinating centre, The George Institute for Global Health.

We compared characteristics of participants at baseline across the aforementioned eGFR and UACR categories. We used the inverse variance weighted method to calculate the weighted

pooled mean and standard deviation for continuous variables and pooled number and proportions for categorical variables.

Treatment effects on clinical outcomes were estimated in individual trials using Cox regression models with covariate stratification as pre-specified in each trial. We obtained summary effect estimates, overall and according to baseline eGFR and UACR by pooling log-transformed hazards ratios using inverse variance weighted averages. We assessed effect modification across ordered eGFR, UACR and KDIGO risk categories using Cochran-Armitage tests for trend..

Consistent with our previous work, we used a two-slope mixed-effects linear spline model with an unstructured covariance matrix for eGFR slope analyses. Acute, chronic and total slopes were defined based on this two-slope model, with a knot placed at the first eGFR value after randomization. Models included two-way and three-way interaction terms between randomized treatment, eGFR or UACR, and the two-slope linear spline for follow-up time. A detailed description of these methods, including worked examples for calculating eGFR slope as used in SMART-C publications, is publicly available on GitHub (https://github.com/SGLT2-Trialists-Consortium/egfr-slope). For all eGFR slope analyses, we report both relative effects (percentage change) and absolute effects (mL/min/1.73m²/year). Because absolute effects on chronic and total eGFR slopes are influenced by the underlying rate of CKD progression, any observed heterogeneity in absolute effects may reflect differences in baseline risk and may not be generalizable. As our primary aim was to assess effect modification by eGFR and UACR, we focused on relative effects for chronic eGFR slope, which are also more likely to be generalizable to routine clinical populations. Relative acute effects were calculated by dividing the absolute treatment effect and its 95% confidence interval by the mean baseline eGFR, while relative effects on chronic eGFR scope were calculated by dividing the absolute treatment effect and its 95% confidence interval by the rate of eGFR decline in the placebo

arm. This approach is consistent with our previous work,[25] and the accompanying companion meta-analysis.[10]

Effect estimates on eGFR slope in individual trials were meta-analyzed using the approach described previously, with Cochran-Armitage tests for trend used to evaluate heterogeneity across ordered eGFR, UACR and KDIGO subgroups.

All analyses including clinical outcomes and eGFR slope were conducted using an intention-to-treat approach. All P values were two-sided with values <0.05 considered statistically significant. Trial-level meta-analysis was performed using R version 4.3.1.

Results

The meta-analysis included 70,361 participants enrolled in 10 randomized, double-blind, placebo-controlled trials (Table S1). Risk of bias was low in all trials (Table S2). Characteristics of participants across eGFR and UACR categories are displayed in Table 1. In lower eGFR categories, participants were more likely to have UACR >300 mg/g and less likely to have atherosclerotic cardiovascular disease or diabetes, reflecting that those with reduced eGFR were predominantly enrolled from CKD trials. Similarly, in higher UACR categories, participants were more likely to have eGFR <45 mL/min/1.73m², be male, and were less likely to have atherosclerotic cardiovascular disease or diabetes.

Overall, 2,314 (3.3%) participants experienced the primary outcome of CKD progression, and 5,739 (8,2%) experienced CKD progression or death due to cardiovascular causes. 988 (1.4%) reached kidney failure, and 6,996 (9.9%) reached kidney failure or died due to any cause. 1,344 (1.9%) participants had serious AKI.

The incidence of the primary outcome of CKD progression was lower with SGLT2 inhibitors compared to placebo (40.3 vs. 25.4 events per 1000 patient-years; HR 0.62, 95% CI 0.57–

0.68). SGLT2 inhibitors also lowered the risks of all secondary kidney outcomes studied, including CKD progression or cardiovascular death (HR 0.75, 95% CI 0.72-0.80), kidney failure alone (HR 0.66, 95% CI 0.58-0.75), kidney failure or all-cause mortality (HR 0.85, 95% CI 0.81-0.89) and serious AKI (HR 0.74, 95% CI 0.66-0.82) (Figure S2).

The effect of SGLT2 inhibitors on CKD progression was similar across eGFR categories: ≥60 (HR 0.61, 95% CI 0.52–0.71), 45–<60 (HR 0.57, 95% CI 0.47–0.70), 30–<45 (HR 0.64, 95% CI 0.54–0.75), and <30 mL/min/1.73 m² (HR 0.71, 95% CI 0.60–0.83; P-trend=0.16; Figure 1). In an exploratory analysis, the effect was also consistent when we divided participants with stage 4 CKD into eGFR 20-30 mL/min/1.73m^2 and <20 mL/min/1.73m^2, although there were only 254 (0.4%) participants in the <20 mL/min/1.73m^2 subgroup (P-trend=0.12; Figure S3). In analyses further stratified by diabetes status, there was no evidence that the effect of SGLT2 inhibitors on CKD progression was modified by eGFR in participants with diabetes (P-trend=0.39) or those without diabetes (P-trend=0.57) (Figure 1).

SGLT2 inhibitors reduced risk of CKD progression regardless of baseline UACR, with benefit in participants with UACR ≤30 (HR 0.58, 95% CI 0.44-0.76), >30-300 mg/g (HR 0.74 (95% CI 0.57-0.96) and >300 mg/g (HR 0.57, 95% CI 0.52-0.64; P-trend=0.49; Figure 2). In analyses treating participants with and without diabetes separately, again there was no evidence of effect modification by baseline UACR in either population (P-trend=0.96 and 0.07 for diabetes and non-diabetes, respectively; Figure 2), though there were very few events in participants without diabetes and UACR ≤30 mg/g. SGLT2 inhibitors reduced the risk of CKD progression irrespective of KDIGO risk categories, overall and in participants with and without diabetes (Figure S4).

SGLT2 inhibitors induced an acute decline in eGFR (relative change −5%, 95% CI −4.7 to −5.2; absolute change −2.19 mL/min/1.73 m², 95% CI −2.31 to −2.08; Figure 3). In relative terms, this acute reduction was more pronounced at lower baseline eGFR (P-trend <0.001),

whereas in absolute terms, the decline was attenuated at lower baseline eGFR (P-trend =0.01; Figure S5). The relative acute effect was also greater in participants with higher UACR, likely reflecting the lower mean baseline eGFR across higher UACR categories (Figure 3). Acute effects across KDIGO risk categories, and absolute effects across subgroups, are shown in Figures S5-6.

SGLT2 inhibitors reduced the annual rate of eGFR decline (relative difference -51%, 95% CI -54 to -49; absolute difference 1.26 mL/min/1.73m^2/year, 95% CI 1.20-1.32; Figure 4). Although there was some evidence that the magnitude of benefit varied across eGFR and UACR categories (P-trend=0.02 and 0.002, respectively) there was clear and separate benefit for all eGFR and UACR subgroups, including eGFR <30 mL/min/1.73m^2 (-47%, 95% CI -59 to -34) and UACR ≤30 mg/g (-54%, 95% CI -58 to -50) (Figure 4). Since the rate of eGFR decline increased with increasing UACR, absolute effects were generally largest in participants with UACR >300 mg/g (Figure S7). Patterns were similar across eGFR and UACR subgroups stratified by diabetes status (Figure 4), KDIGO risk categories (Figure S8) and when evaluating total eGFR slope (Figure S9).

There was some evidence that the reduction in serious AKI with SGLT2 inhibitors was attenuated in partcipants with eGFR <30 mL/min/1.73m^2 (P-trend=0.02) but this effect was consistent regardless of UACR (P-trend=0.49, respectively; Figure S10).

Discussion

In this large, collaborative meta-analysis using individual participant data, we observed reductions with SGLT2 inhibitors for all kidney outcomes studied, including kidney failure alone. Importantly, SGLT2 inhibitors lowered the risk of CKD progression across the full spectrum of eGFR and UACR, including among participants with eGFR <30 mL/min/1.73m^2 and those with little to no albuminuria, for whom current guidelines offer weaker recommendations. While few clinical outcomes were observed in participants without diabetes

and with normal levels of albuminuria, analyses of eGFR slope, a more sensitive, continuous outcome, demonstrated clear benefits on kidney function decline across all eGFR and albuminuria subgroups. This was also true when participants with and without diabetes were assessed separately, and regardless of whether eGFR slope was expressed as relative or absolute differences. These findings, representing the totality of the large-scale randomized evidence for SGLT2 inhibitors approved for reducing CKD progression, provide the clearest support to date for routine use of SGLT2 inhibitors across the full spectrum of CKD, including in patients with stage 4 CKD, who are at the highest risk of kidney failure, and in those with little to no albuminuria.

Our findings reinforce recommendations from major cardiovascular, endocrinology and nephrology clinical practice guidelines to initiate SGLT2 inhibitors in patients with CKD and an eGFR ≥20 mL/min/1.73 m^2, regardless of diabetes.[2,27,28] Data from over 27 million individuals in the CKD Prognosis Consortium indicate that patients with stage 4 CKD (eGFR <30 mL/min/1.73 m^2) are at between 110 to 580 times higher risk of kidney failure (depending on level of albuminuria) compared to those with eGFR ≥90 mL/min/1.73m^2 and with normal albuminuria.[29] Uptake of SGLT2 inhibitors among those with stage 4 CKD has been limited, partly because the level of evidence provided by this collaborative meta-analysis was not previously available, but also because of the continuing perception of SGLT2 inhibitors as glucose-lowering agents, whose glycosuric effect is almost completely abrogated at this level of kidney function.[30] Additionally, there were residual concerns regarding the safety in this population because of the relatively limited number of participants with stage 4 CKD enrolled in individual trials. This meta-analysis identified no increased risk of serious AKI, even amongst those with stage 4 CKD. The overall reduction in serious AKI indicates a strong case for updating labelling on AKI risk with SGLT2 inhibitors, which may help to assuage any remaining concerns about their safety in patients with stage 4 CKD. Better treatment for this very-high risk group offers a major opportunity to reduce the individual and societal burden of kidney failure.

Equally important, the clear kidney benefits observed in patients across the spectrum of albuminuria suggest that guidelines that offer weaker recommendations for patients with lower levels of albuminuria should be updated. Our results extend a 2019 meta-analysis that reported no effect modification by baseline albuminuria,[31] now in a much larger and broader population, including those without diabetes. Patients with severely increased albuminuria (UACR >300 mg/g) are at highest risk of CKD progression and the absolute benefits of SGLT2 inhibitors are largest in these individuals. However, the National Health and Nutrition Examination Survey estimates that 8.6% of adults in the United States have a UACR of 30–300 mg/g while only 1.6% have a UACR >300 mg/g. Treating the *five-fold* larger population in the United States with moderately increased albuminuria may deliver large additional health gains. The same is likely to be true in many other geographical regions where lower levels of albuminuria represent the majority of cases of CKD.[32] When initiated in early-stage CKD, renin-angiotensin system blockade has been shown to provide more years free from kidney failure compared with intervention in advanced CKD.[33] Taken together, more widespread implementation of SGLT2 inhibitors in patients with lower levels of albuminuria and early-stage CKD, particularly those with concomitant diabetes, could have substantial benefits in preventing kidney function decline at a population level. Nevertheless, we recognize that rates of CKD progression observed in trial populations, such as those included in this meta-analysis, are not necessarily generalizable to routine care. When considering the broader benefits of SGLT2 inhibitors on hospitalization and mortality outcomes, as summarized in the accompanying companion study,[10] the totality of the available evidence indicates that the direct economic benefits to health systems are likely to be considerable, since SGLT2 inhibitors are already available as generics in several countries, with patent expiry expected in most jurisdictions within the next few years. Economic evaluation in different settings may provide important information for policymakers and health systems.

The acute reductions in eGFR sumamrised in this meta-analysis are modest across all eGFR and UACR subgroups and considerably smaller than the 20-30% threshold at which temporary treatment discontinuation is recommended in clinical practice guidelines.[2] While relative effects are most informative for evaluating long-term outcomes, acute declines in eGFR are typically viewed as a safety consideration and are therefore more commonly interpreted in absolute terms. The smaller absolute reductions observed at lower baseline eGFR resemble the pattern seen with renin–angiotensin system blockade.[34] Our findings should reassure clinicians that these effects are minimal at lower GFR and should not preclude treatment initiation.

Limitations

The findings from this collaborative meta-analysis have some limitations. First, data on the effects of SGLT2i in patients with eGFR <20 mL/min/1.73m^2 was limited to one trial – EMPA-KIDNEY – precluding recommendations to initiate therapy below current thresholds. The RENAL LIFECYCLE trial will address this gap by evaluating dapagliflozin versus placebo in approximately 1500 patients with eGFR <25 mL/min/1.73m², kidney failure requiring dialysis, or kidney transplant recipients.[35] Second, despite pooling of data across 10 trials, the number of primary outcome events was limited among participants without diabetes and with normal albuminuria (UACR <30 mg/g), reducing the statistical power to assess effect modification by albuminuria separately in patients without diabetes, though the use of the continuous outcome of eGFR slope provided better power to assess effects on kidney function in these individuals. Third, the distribution of albuminuria across eGFR subgroups in this meta-analysis reflects the entry criteria of the included trials and may not mirror routine clinical practice (e.g., most participants with advanced CKD had severely increased albuminuria). Importantly, however, the consistent effects across eGFR, UACR, and KDIGO risk categories support the generalizability of these relative effect estimates to broader CKD populations in clinical care. Fourth, while we did not conduct a one-stage meta-analysis, our individual participant-level

approach to harmonizing outcomes is consistent with methods used by other large cardiometabolic consortia.[29]

Conclusions

In summary, SGLT2 inhibitors lower the risk of CKD progression regardless of baseline eGFR or albuminuria, reduce serious acute kidney injury and kidney failure. These data provide strong support for their routine use to improve kidney outcomes across the spectrum of kidney function and albuminuria among patients with type 2 diabetes, CKD or heart failure.

CONTRIBUTIONS

BLN & HJLH conceived the meta-analysis and developed its analytical strategy. BLN and HJLH serve as Secretariat of SMART-C (www.smart-c.net). BLN and HJLH are responsible for the decision to submit for publication. RAF performed the meta-analysis. BLN and HJLH wrote the first draft of the manuscript. All authors contributed to interpretation and manuscript review.

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VP serves as a board director for St Vincent's Health Australia, Victor Chang Cardiac Research Institute, and Mindgardens; and has received honoraria for Steering Committee roles, scientific presentations, or advisory board attendance, or a combination, from Abbvie, Amgen, Astra Zeneca, Bayer, Baxter, Boehringer Ingelheim, Chinook, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Otsuka, Pharmalink, Pfizer, Reata, Travere, Relypsa, Roche, Sanofi, Servier, and Tricida.

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DATA SHARING & OPEN ACCESS

Detailed information on data sharing policies for the individual trials included within SMART-C are available in the primary publication of each relevant trial.

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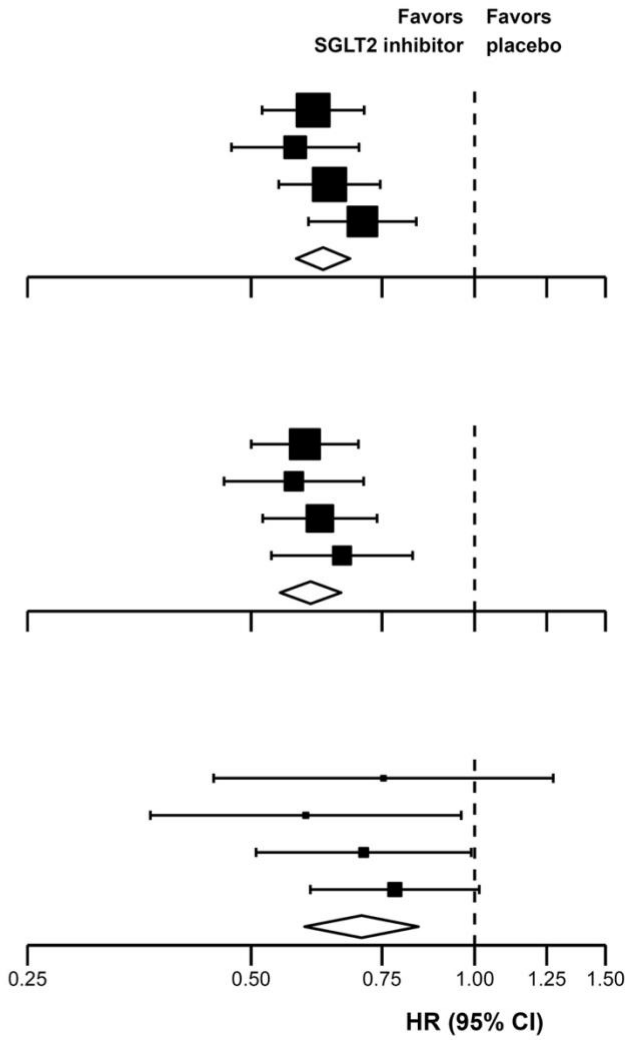
Table 1. Characteristics of participants at baseline according to eGFR and UACR at randomization in the 10 included trials.

	eGFR (mL/min/1.73m^2)				UACR (mg/g)		
	<30 (n=3895)	30 to <45 (n=10891)	45 to <60 (n=12167)	≥60 (n=43147)	≤30 (n=29767)	>30 to 300 (n=14176)	>300 (n=14873)
Age, years, mean (SD)	67.9 (11.5)	69.4 (9.8)	68.8 (8.6)	63.5 (8.0)	64.6 (7.8)	65.4 (8.6)	62.7 (10.2)
Male, n (%)	2485 (63.8)	6836 (62.8)	7804 (64.1)	28442 (65.9)	18356 (61.7)	9667 (68.2)	10250 (68.9)
Female, n (%)	1410 (36.2)	4055 (37.2)	4363 (35.9)	14705 (34.1)	11411 (38.3)	4509 (31.8)	4623 (31.1)
Race							
Asian	1053 (27.0)	2629 (24.1)	2511 (20.6)	7530 (17.5)	4018 (13.5)	2815 (19.9)	4472 (30.1)
Black	174 (4.5)	460 (4.2)	493 (4.1)	1742 (4.0)	1181 (4.0)	615 (4.3)	668 (4.5)
White	2504 (64.3)	7324 (67.2)	8585 (70.6)	32042 (74.3)	23437 (78.7)	10224 (72.1)	8801 (59.2)
Other	164 (4.2)	463 (4.3)	561 (4.6)	1805 (4.2)	1096 (3.7)	505 (3.6)	926 (6.2)
Medical history							
Atherosclerotic cardiovascular disease, n (%)	1687 (43.3)	6023 (55.3)	7831 (64.4)	25649 (59.4)	18512 (62.2)	8920 (62.9)	6931 (46.6)
Diabetes, n (%)	2262 (58.1)	6961 (63.9)	8369 (68.8)	36558 (84.7)	25829 (86.8)	11748 (82.9)	11369 (76.4)
Heart failure, n (%)	959 (24.6)	4186 (38.4)	5579 (45.9)	12982 (30.1)	6645 (22.3)	3614 (25.5)	2364 (15.9)
Systolic BP	135.9 (18.2)	133.0 (17.0)	132.2 (16.1)	133.3 (15.8)	132.2 (15.1)	135.2 (16.1)	140.1 (16.9)
Estimated GFR, mL/min/1.73m^2							
≥60	..	..	..	43147	23435 (78.7)	8612 (60.8)	4652 (31.3)
45 to <60	..	..	12167	..	3353 (11.3)	2372 (16.7)	3518 (23.7)
30 to <45	..	10891	..	..	2195 (7.4)	2231 (15.7)	4524 (30.4)
<30	3895	..	..	..	614 (2.1)	901 (6.4)	2161 (14.5)
UACR, mg/g							
≤30	614 (15.8)	2195 (20.2)	3351 (27.5)	23433 (54.3)	29767	..	..
>30 to 300	901 (23.1)	2231 (20.5)	2374 (19.5)	8614 (20.0)	..	14176	..
>300	2161 (55.5)	4524 (41.5)	3518 (28.9)	4652 (10.8)	..	..	14873
RAS blockade, n (%)	3218 (82.6)	9481 (87.1)	10643 (87.5)	35837 (83.1)	24085 (80.9)	11819 (83.4)	13756 (92.5)

Race was self-reported in all trials. Atherosclerotic cardiovascular disease was defined as a history of coronary artery disease, peripheral artery disease or cerebrovascular disease. Diabetes status was based on investigator reported medical history. History of heart failure was based on investigator reported medical history (outside of the dedicated heart failure trials). eGFR: estimated glomerular filtration rate; UACR: urinary albumin-to-creatinine ratio; SD: standard deviation; ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; RAS: renin angiotensin system.

Figure 1. Effects of SGLT2i on CKD progression according to baseline eGFR, overall and by diabetes status.

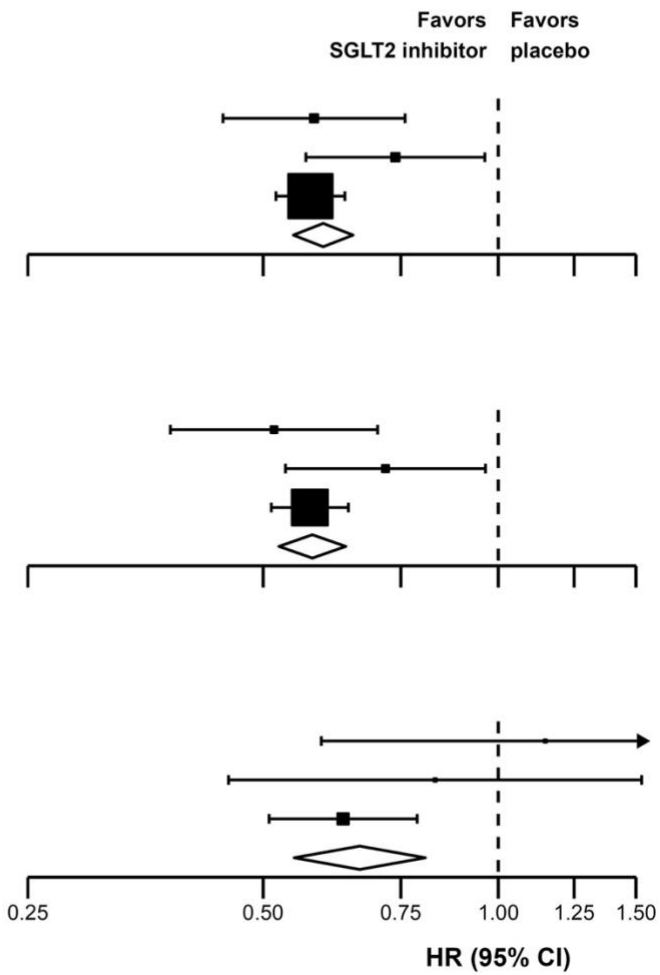
Baseline estimated GFR (mL/min per 1.73m^2)	SGLT2 inhibitor	Placebo	HR (95% CI)
	no. / total no. (%)		
All			
≥60	271/23,164 (1.2)	369/19,951 (1.8)	0.61 (0.52−0.71)
45 to <60	164/6255 (2.6)	273/5902 (4.6)	0.57 (0.47−0.70)
30 to <45	274/5561 (4.9)	389/5323 (7.3)	0.64 (0.54−0.75)
<30	241/1928 (12.5)	333/1966 (16.9)	0.71 (0.60−0.83)
Overall	950/36,911 (2.6)	1364/33,146 (4.1)	0.62 (0.57−0.68)
Trend by baseline estimated GFR: p = 0.16			
Diabetes			
≥60	246/19,861 (1.2)	335/16,665 (2.0)	0.59 (0.50−0.70)
45 to <60	137/4355 (3.1)	226/4004 (5.6)	0.57 (0.46−0.71)
30 to <45	213/3586 (5.9)	306/3368 (9.1)	0.62 (0.52−0.74)
<30	139/1122 (12.4)	199/1105 (18.0)	0.66 (0.53−0.82)
Overall	735/28,940 (2.5)	1066/25,165 (4.2)	0.60 (0.55−0.66)
Trend by baseline estimated GFR: p = 0.39			
No diabetes			
≥60	25/3303 (0.8)	34/3286 (1.0)	0.75 (0.45−1.28)
45 to <60	27/1900 (1.4)	47/1898 (2.5)	0.59 (0.37−0.96)
30 to <45	61/1975 (3.1)	83/1955 (4.2)	0.71 (0.51−0.99)
<30	102/788 (12.9)	134/837 (16.0)	0.78 (0.60−1.01)
Overall	215/7971 (2.7)	298/7981 (3.7)	0.70 (0.59−0.84)
Trend by baseline estimated GFR: p = 0.57			



Includes data from 10 trials. Box sizes are inversely proportional to the standard error of the treatment effect. CKD progression defined as ≥50%reduction in estimated glomerular filtration rate, kidney failure or death due to kidney failure. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SGLT2: sodium-glucose cotransporter 2; HR: hazard ratio; CI: confidence interval.

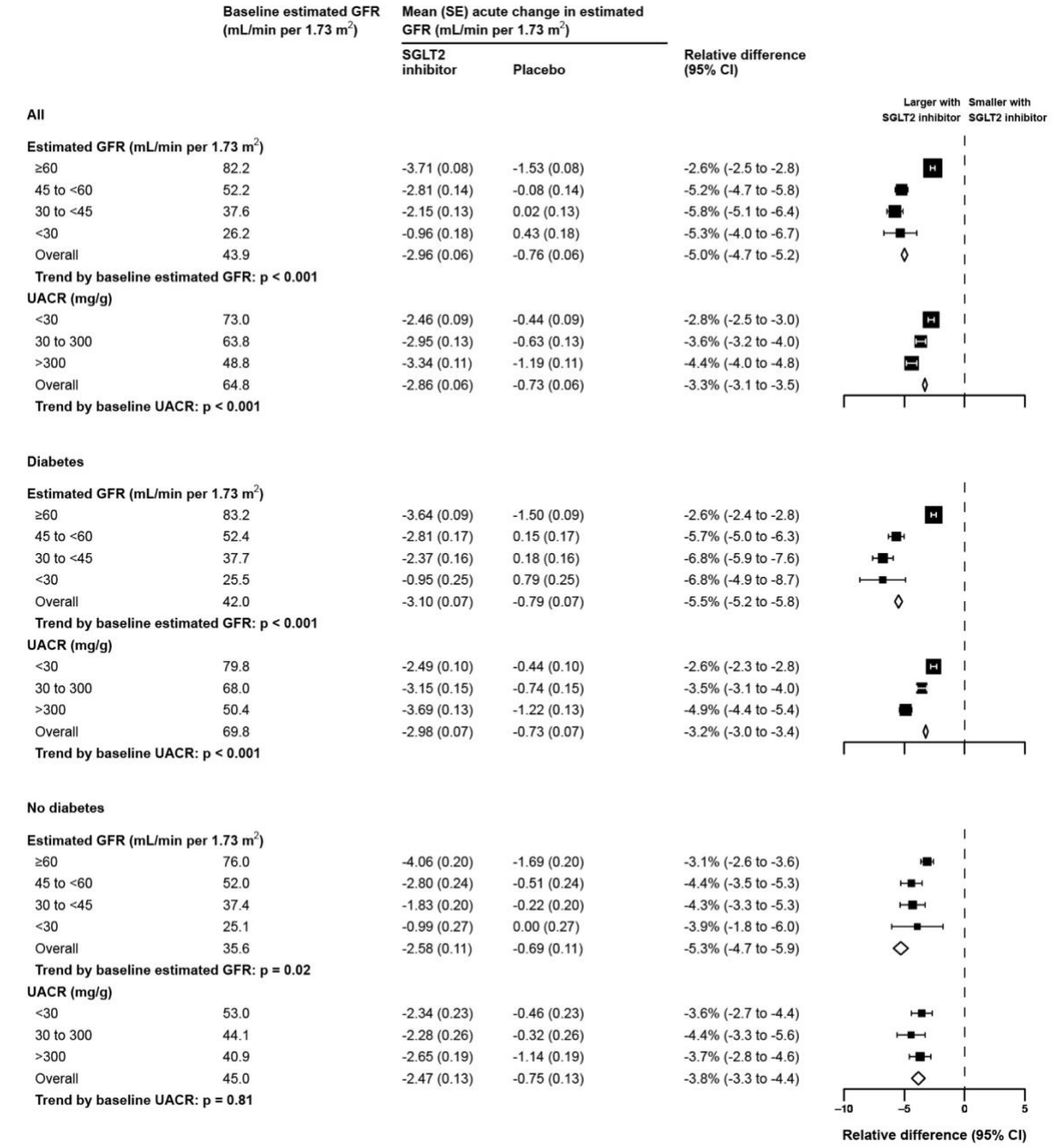
Figure 2. Effects of SGLT2i on CKD progression according to baseline UACR, overall and by diabetes status.

Baseline UACR, mg/g	SGLT2 inhibitor	Placebo	HR (95% CI)
	no. / total no. (%)		
All			
<30	94/15,973 (0.6)	125/13,595 (0.9)	0.58 (0.44−0.76)
30 to 300	109/7583 (1.4)	128/6519 (2.0)	0.74 (0.57−0.96)
>300	637/7575 (8.4)	999/7275 (13.7)	0.57 (0.52−0.64)
Overall	843/31,407 (2.7)	1252/27,644 (4.5)	0.60 (0.55−0.65)
Trend by baseline UACR: p = 0.49			
Diabetes			
<30	73/13,984 (0.5)	108/11,645 (0.9)	0.52 (0.38−0.70)
30 to 300	89/6365 (1.4)	103/5309 (1.9)	0.72 (0.53−0.96)
>300	503/5849 (8.6)	786/5497 (14.3)	0.57 (0.51−0.64)
Overall	668/26,464 (2.5)	997/22,696 (4.4)	0.58 (0.52−0.64)
Trend by baseline UACR: p = 0.96			
No diabetes			
<30	21/1988 (1.1)	17/1950 (0.9)	1.15 (0.59−2.22)
30 to 300	20/1218 (1.6)	25/1210 (2.1)	0.83 (0.45−1.53)
>300	134/1726 (7.8)	213/1778 (12.0)	0.63 (0.51−0.79)
Overall	175/4943 (3.5)	255/4948 (5.2)	0.66 (0.55−0.81)
Trend by baseline UACR: p = 0.07			



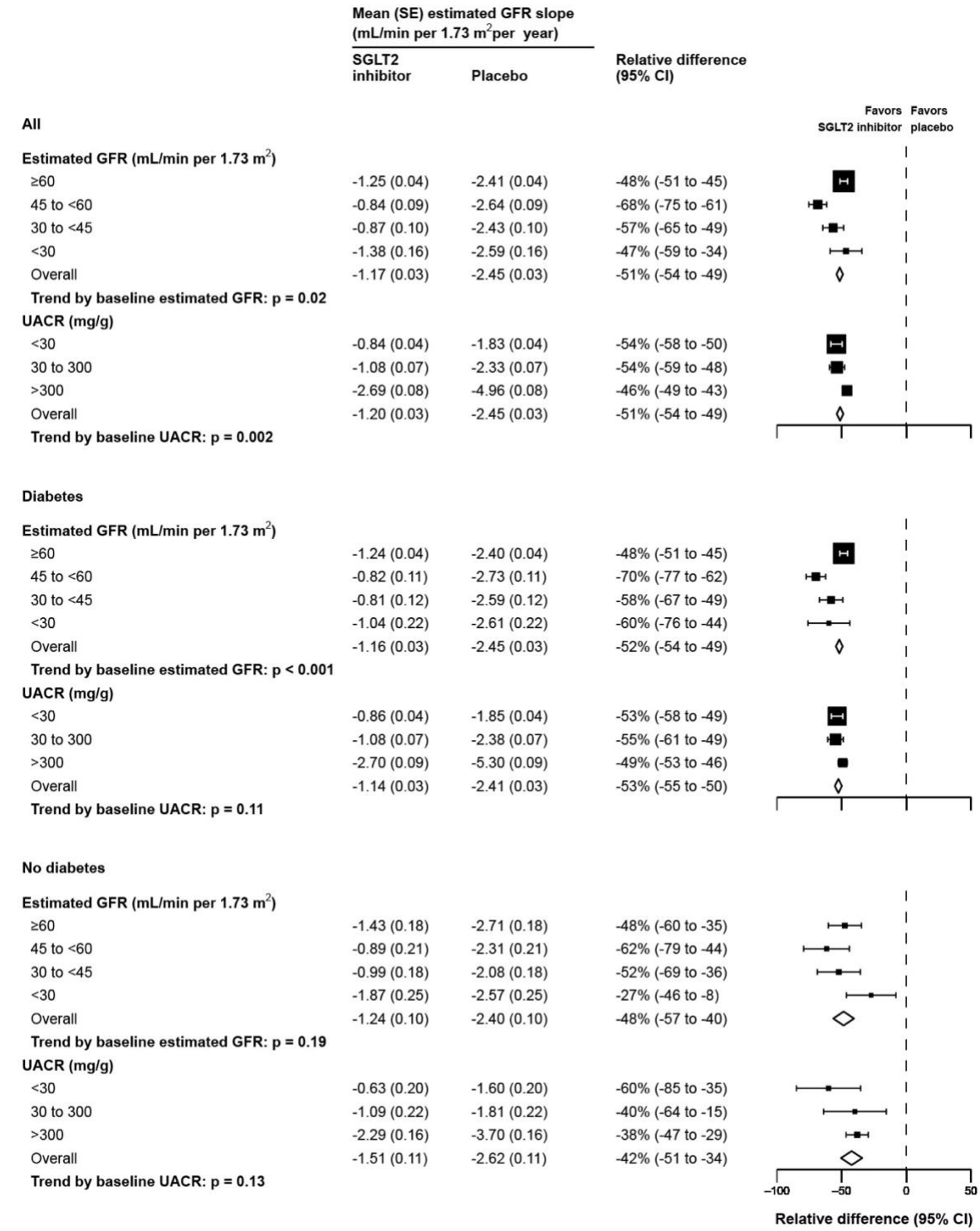
Includes data from 8 trials. Box sizes are inversely proportional to the standard error of the treatment effect. CKD progression defined as ≥50%reduction in estimated glomerular filtration rate, kidney failure or death due to kidney failure. CKD: chronic kidney disease; UACR: urinary albumin:creatinine ratio; SGLT2: sodium-glucose cotransporter 2; HR: hazard ratio; CI: confidence interval.

Figure 3. Effects of SGLT2i on acute changes in eGFR according to baseline GFR and UACR, overall, and by diabetes status.



eGFR subgroups include data from 10 trials, while UACR subgroups include data from 8 trials. Box sizes are inversely proportional to the standard error of the treatment effect. eGFR: estimated glomerular filtration rate; UACR: urinary albumin:creatinine ratio; SGLT2: sodium glucose cotransporter 2; SE: standard error; CI: confidence interval.

Figure 4. Effects of SGLT2i on chronic eGFR slope according to baseline eGFR and UACR, overall, and by diabetes status.



eGFR subgroups include data from 10 trials, while UACR subgroups include data from 8 trials. Box sizes are inversely proportional to the standard error of the treatment effect. eGFR: estimated glomerular filtration rate; UACR: urinary albumin:creatinine ratio; SGLT2: sodium glucose cotransporter 2; SE: standard error; CI: confidence interval.

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